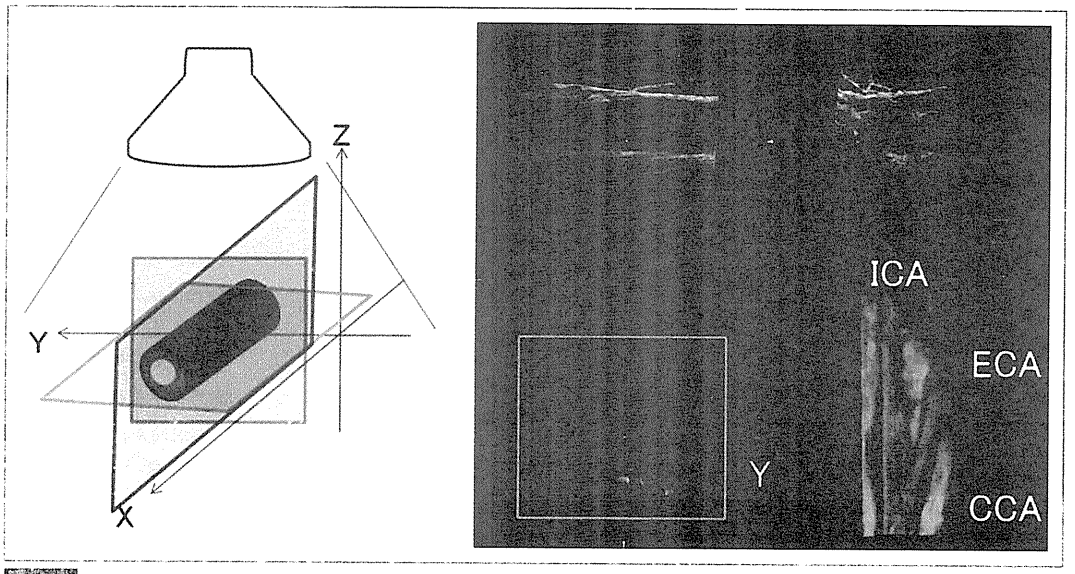

図4 プローブ内の探触子が高速に機械的に動き3D情報（X軸，Y軸，Z軸の画像）を得てから，オフラインでvolume rendering法を用いて3D画像を構築（右下図）

の報告があり[7]，数多くの報告でその有用性が示されてきている．一方，現時点の問題点としては，機械が高額であり一般的な普及がまだまだであること，プローベのサイズが大きいこと，石灰化病変の評価が不十分であること，アーチファクトが大きいことなどがあげられる．

他画像参照システム

次に，MRIなどの画像検査をリアルタイムに参照しながら超音波検査を行うのが他画像参照システムであり，具体的には，GPSシステムのように磁場装置を用いて位置情報をもたせた上での超音波検査である．そのようにすることで，超音波検査の特徴である低侵襲でリアルタイムに繰り返し施行可能であることと，MRIの特徴である再現性に優れ術者の手技に依存しないことといった，両者の特徴を活かしながら検査可能であると考えられる．図3に当院における実際の施行の様子を示す．当院では超音波装置にGE Healthcare製Logic E9とリニアやコンベックスプローベを用いて行っている．このシステムは当初は肝臓，腎臓，前立腺，乳腺などの超音波のみでは困難な深部病変の診断や

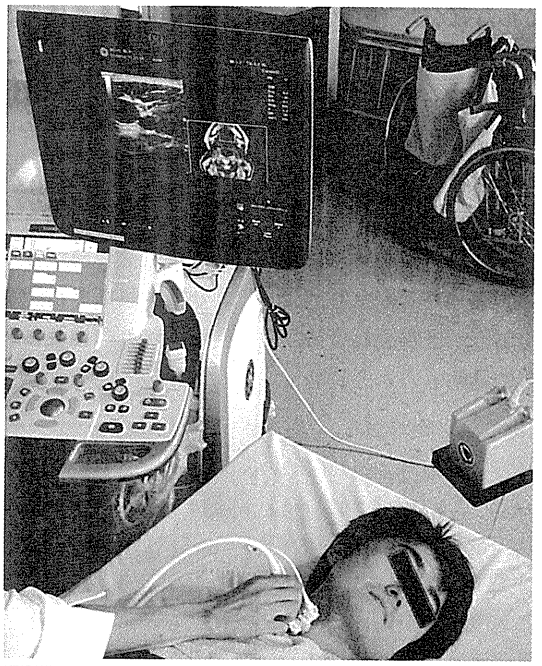

図3 他画像参照システムの測定の実際．Logic E9とリニアプローベを使用

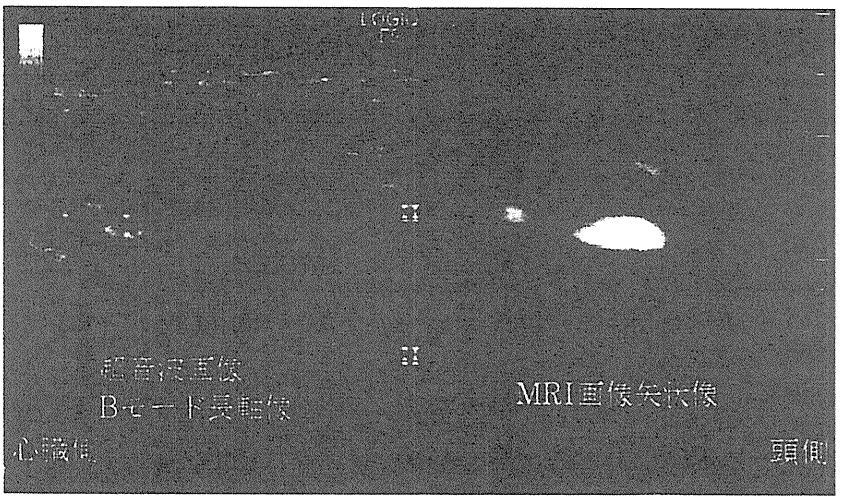

図4 内頸動脈狭窄症症例でMRI画像（MPRAGE）をリアルタイムに参照しながら超音波検査を施行している際の実際の他画像参照システムの画像

治療に用いられてきたが[8]，当院では頸動脈領域での詳細なプラークの観察などへ応用を開始している．図4は頸部MRI（MPRAGE画像）を参照画像として頸動脈超音波検査を行っている一場面であるが，プローベの走査に合わせて短軸画像から長軸画像に移行してもリアルタイムにMRI画像が連動し，MRI画像で粥腫と判断された部分が頸動脈超音波検査でどのように見えるのかを比較可能であった．

おわりに

このように近年の超音波装置の進歩に伴って，超音波は頸動脈領域でも進歩が著しく，3D超音波や他画像参照システムを含めて脳卒中領域においても超音波による診断や治療は急速に進歩を遂げている．今後も超音波装置の進歩が予測され，ますます超音波が重要になってくると考えられる．検者側も十分に原理や目的，手法を理解することで，さらによりよい診断や治療につながる超音波検査が可能になると考えられる．

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経頭蓋ドプラ

東京都保健医療公社大久保病院神経内科/東京女子医科大学神経内科 堤 由紀子 Tsutsumi Yukiko
〒160-8488 東京都新宿区歌舞伎町 2-44-1

はじめに

経頭蓋超音波ドプラ法（transcranial Doppler：TCD）は，パルスドプラ法を用いて頭蓋内血管の血流を測る装置である．ベッドサイドで行える検査のため，くも膜下出血の血管攣縮（れんしゅく）判定や頭蓋内血管狭窄，閉塞の診断に用いられる．神経内科領域では，頚動脈狭窄例での栓子シグナルの検索，若年者脳梗塞の原因検索にバブル法を用いた右左短絡の証明（コントラストTCD），rt-PA投与時の血管再開通の評価がおもな使用方法である．

しかし，頭蓋骨の超音波透過性は，加齢とともに低下し，高齢女性ではほとんど透過しない[1]．経頭蓋ドプラ検査を初めて行うときは，血流が描出されないと，自分の技術が未熟なのか，超音波が骨を通過しないのか判断できず，長時間を費やしてしまいがちである．実際にせっかくの装置が放置されている施設もある．

そのため，本稿では経頭蓋ドプラ検査のコツを説明する．TCDの一般的な方法と概要は，日本脳神経超音波学会の頭蓋内超音波検査ガイドライン[2]や脳神経超音波マニュアル[3]を参考にしてほしい．

方 法

①経頭蓋カラードプラ法（transcranial color flow imaging：TC-CFI）専用，または心臓用の汎用セクタプローブ（探触子）で，2MHzに設定し，側頭骨窓（**図1**）から観察する．対側の側頭骨が観察されれば（**図2**），超音波が骨を通過している証拠である．次に，カラードプラをかけて血管がきれいに描出される側頭骨窓を探す．血管が描出されたら，何cmの深さで見えるかチェックする．反対側の頭蓋骨が見えなければ，骨を通過しない大後頭孔経路に変更する．

②経頭蓋ドプラでは，マルチウインドウの装置（いろいろな深さで同時に描出できる，**図3**）ならば，血管を検出しやすい．マルチウインドウでなければ，先程の血管が描出できた深さで検索する．

③頚動脈狭窄や心原性脳塞栓症の栓子シグナルの検出には，TCDの専用モードでモニタリングを行うが，マイクロバブル法による右左短絡の診断は，プローブの固定に時間がかかるので，もう一人の検者にプローブを押さえてもらう．

TCDプローブの固定バンドでの固定は20～30分位かかることも少なくないため，固定が困難な場合は交代で，プローブを手で固定する．ちなみに，当施設（東京女子医科大学神経内科）では，はじめにプローブを当ててから固定が終わるまで30分以内にできるようにしている．それ以上かかる場合は諦めて手で固定するか，

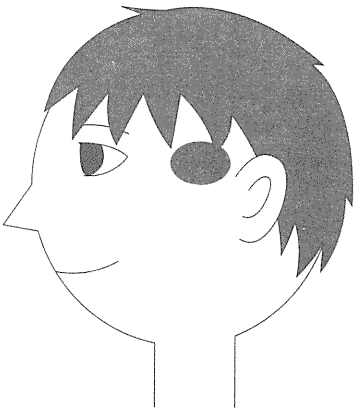

図１　側頭骨窓
耳介の前方部分は側頭骨窓(temporal window）と言い，骨の薄い部分．

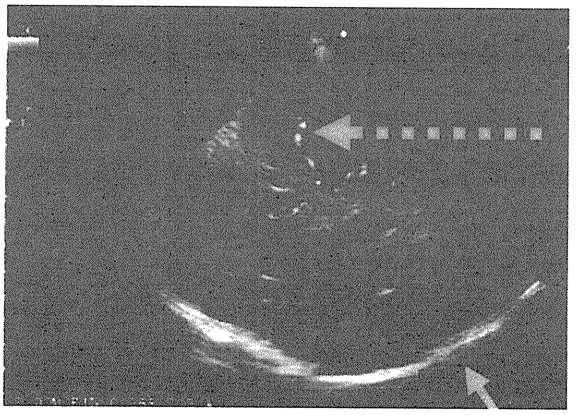

図２　経頭蓋カラーフローイメージング
対側の側頭骨（➡），中大脳動脈（middle cerebral artery, ➡）．

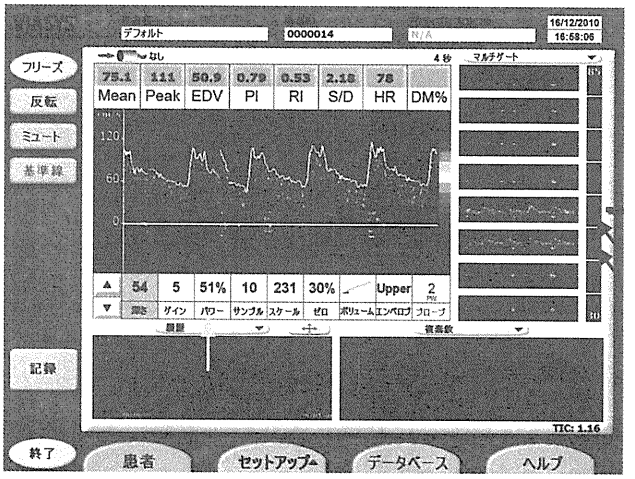

図３　Care Fusion 社；SONARA モニター画面
右のマルチゲートで，側頭骨から深さ 30mm から 85mm の 7mm 間隔で 8 箇所の血流波形を出している．一番血流波形が描出されるところで，栓子シグナルのモニターを行う（この症例では 43mm と 50mm のいずれか［➡］）．
大後頭孔経由では，骨を通さず直接超音波が頭蓋内に入るため，血流波形がでたら超音波の出力をできるだけ下げるようにする（　）．

大後頭孔からの観察に切り替える．

④大後頭孔からの観察は，骨を通さないので，最低でも椎骨動脈は描出できる．首が短い高齢者では，脳底動脈は描出できないこともある．

⑤総頚動脈や内頚動脈で栓子シグナルを検出する方法もあるが，血管が太く，血流速度も速いため，アーチファクトが多く，比較的小さめな栓子シグナルは血管雑音にかき消されてはっきりしないこともある．このため，細い椎骨動脈で検査することが望ましい．

⑥大後頭孔は，首と後頭部の境界のくぼんだ部位である．そこに側臥位または臥位で頭を横に向けてもらい，後ろからプローブを当てる．深さ 35～75mm 位で遠ざかる血流は椎骨動脈で，75mm 以上の深さで遠ざかる血流は脳底動脈である．

⑦一般的な施設では臥位で行っているが，外来での検査では座位で行うことも可能である．ドイツではドプラ波形を頭蓋内すべて観察する場合は臥位で，頚動脈狭窄の栓子シグナル検索は座位で行っていた．このため，狭い外来診察室でも座位なら検査が可能である．

栓子シグナル

近年のTCD装置は栓子シグナルの自動解析ソフトを携帯している．アーチファクトか空気か血栓（栓子）の鑑別をしてくれるが，高価なため購入が困難な施設も多い．熟練した検者は，自動解析ソフトは参考にするだけで，自分の耳で聞いた音で判断している．このため，自動解析ソフトのない機種でも栓子シグナル音（Chirp音［ピュッ，ポッ，ピコッなど］）がわかれば検査が可能である．検査時間はガイドラインでは30分と記載されている[4]．

コントラストTCD

マイクロバブル法による右左短絡（卵円孔開存または肺動静脈瘻）のTCDによる診断は，短時間で，侵襲なく行える最も有用な検査の一つである．当施設でも，外来の若年者脳梗塞症例の原因検索のルーチン検査である．経食道心エコーと右左短絡の検出頻度はほぼ同等[5]で，侵襲はなく，また一つでも栓子シグナルが検出されれば，右左短絡と診断できるので，false positive（偽陽性）はない．

右上肢の静脈に留置針を挿入し（このときトンボ針なら21G以上の太い針で行ってほしい），三方活栓を装着し10mLのシリンジを二つ装着．生理食塩水または5%ブドウ糖液を6mLから9mLと空気1mLを攪拌し，静脈注射する．

このとき，ジアゼパム（Diazepam［ホリゾン®］）を1滴加えると気泡ができやすくなると報告[6]されているが，経験的に生理食塩水よりもブドウ糖が入っていると良い．本人の血液をラインから血液を引いて1滴加える方法もある．

静注5秒後にバルサルバ負荷をかけて，解除したときに卵円孔は開き，短絡が起きやすい．バルサルバ負荷は，徐脈がおきれば十分に負荷がかかったと判断してよい．徐脈がなければ安静時に何回も練習する．また静脈注射後に右手を挙上して振ると再度バブルが流れる．また，座位で行ったほうが，バルサルバ負荷がかかりやすい．

おわりに

はじめにChirp音がわからなければ，録音して経験豊富なTCD検査の技師や医師に相談するのも一つの手だが，経食道心エコーで卵円孔開存の診断のついた患者にコントラストTCD法を行い，どのような音かを知る方法もある．

TCDは側頭骨経路では，高齢女性は血流波形が描出困難な症例も多く，見えなければ深追いはせずに，大後頭孔経路に変更する．プローブの固定が困難だったら，プローブを手で固定し二人で交互に検査をする．それでも大変なら，すぐにほかの検査にすればよい．

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3．急性脳血管症候群の経頭蓋ドプラ検査

堤　由紀子*
つつみ　ゆきこ

- 経頭蓋ドプラ検査は，プローベの固定に時間を要するので，検者は2人以上のほうがスムーズに行える．
- 卵円孔開存などの奇異性脳塞栓症の診断に，侵襲なく，かつ有効．
- 急性期の頸動脈狭窄では，発症から経頭蓋ドプラ検査までの時間が短いほど栓子シグナルの検出率は高まる．
- 栓子シグナルをモニターすることで，抗血小板薬などの抗血栓薬の効果判定に役立つ．

Key Words　経頭蓋ドプラ，栓子シグナル，奇異性脳塞栓症，頸動脈狭窄，抗血小板薬

一過性脳虚血性発作（TIA）をふくむ急性脳血管症候群では，頸動脈エコーや頭部MRAでの明らかな狭窄や心房細動があればすぐにTIAを疑うが，若年者の場合はTIAを疑うことは困難である．来院時に無症状の場合，経胸壁エコーやホルター心電図は予約するが，侵襲性のある検査は行わないことが多い．このようなとき，経頭蓋ドプラ検査（transcranial Doppler：TCD）は，塞栓症のスクリーニング検査として役立つ．TCDは，海外では頭蓋内血管狭窄の診断や，負荷テストでの血管反応の評価に用いられることが多い．しかし本邦ではMRI・MRA検査や脳血流シンチ検査が一般的になっているため，TCDをこのような検査に用いることは少ない．本邦でTCDの主な使用目的は，頸動脈狭窄など塞栓症が疑われるときの栓子シグナルの検索や，卵円孔開存（patent foramen ovale：PFO）などの右左短絡の診断である．本稿では，TIA患者が来院した場合のTCDの基本的な操作方法と活用方法，最近の文献的なデータを中心に述べる．詳細な活用方法は日本脳神経超音波学会ガイドラインを参照してほしい[1~3]．

□ TCDの操作方法

TCDは**図1**のように一人がプローベを側頭骨窓にあてて，中大脳動脈の血流波形が検出されたところで固定し（①），もう一人がヘッドバンドを固定する（②）．一人ですべて行うと，プローベがずれてしまうため，二人で行ったほうが簡便である．ドプラ波形は**図2**のように，側頭骨から35～60 mmの深さでプローベに向かって立ち上がる血流が中大脳動脈のM1，60～75 mmの深さで遠ざかる血流が前大脳動脈のA1である．A1が見えた深さと位置でプローベをやや後ろ向きに傾けると，向かってくる血流があり，これが後大脳動脈のP1，さらに後ろに傾けると遠ざかる血流のP2が描出される．M1が一番描出しやすいので栓子シグナルの検出はM1の血流速度連続測定で行う．

□ 栓子シグナル

栓子シグナル（embolic signal：ES）は，微小栓子シグナル（microembolic signal：MES）またはHITS（high intensity transient signal）ともいわれ，循環器領域ではHITSのほうがよく知られている．栓子が血管内を通過すると，ドプラ波形上に高信号のシグナル（**図3**）が検出され，血流音のなかにピュッ，ピコッ，ボッなどの特徴的なES音（またはchirp音）を伴う[1]．一般のTCD装置でも，血流音だけでESを聞きわけることも可能だが，ES検出ソフトを搭載している機械では，音の聞こえないESでも検出し，音と周波数解析が記録されるため，後にアーチファクトか栓子かを判断できる．またES音は熟練した検査者でないと聞き逃すことが多い．東京女子医科大学神経内科で，ES解析ソフトを搭載してい

*東京都保健医療公社大久保病院 神経内科，東京女子医科大学医学部 神経内科

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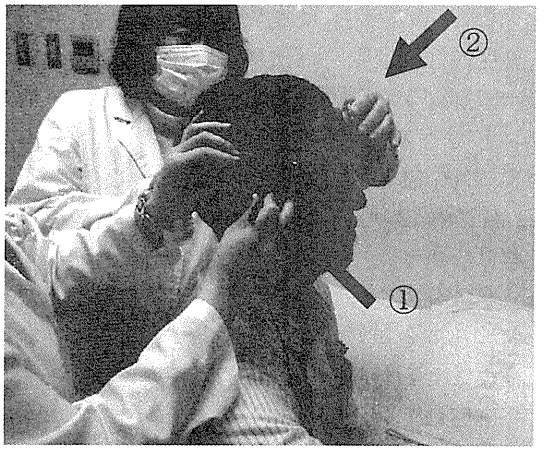

図1　経頭蓋ドプラ装置の固定方法
①一人の検者が側頭骨窓から血流波形が描出されるところでプローベを固定，②もう一人の検者がヘッドバンドを固定する．

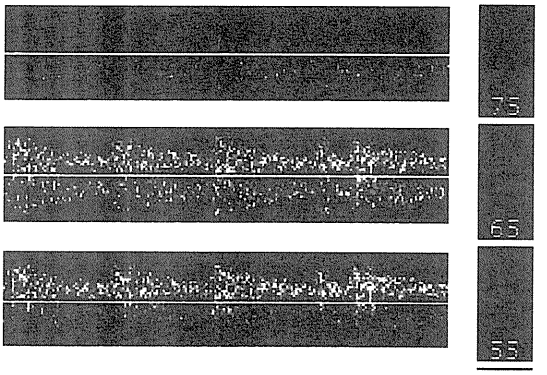

図2　ドプラ波形
①右側の数字は側頭骨からの深さ．②上向きの波形が中大脳動脈（M1）であり，55 mm と 65 mm の深さで明瞭に描出されている．③下向きの波形が前大脳動脈（A1）であり，55 mm よりも深い 65 mm で明瞭に描出．75 mm のさらに深いところでは，M1 はほとんど描出されないが，A1 はわずかに描出されている．

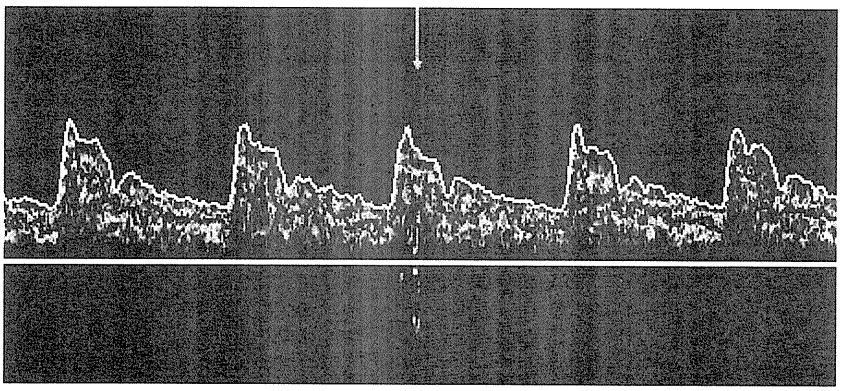

図3　栓子シグナル
ドプラ波形のなかに高信号の部分を認める（矢印）．

る TCD を 1996 年と 2011 年に購入したが，ES 解析能力は格段に進歩しているので，新しい機械なら，初めて検査を行う場合でも ES 検出は容易となっている．ES の検出は，日本脳神経超音波学会ガイドラインでは 30 分の連続血流速度測定と定められている[1]．

□ 奇異性脳塞栓症の TCD での診断方法

静脈系の血栓が，PFO，肺動静脈瘻，心房中隔欠損などの右左短絡を経由して動脈内に流入し脳梗塞を起こす場合を奇異性脳塞栓症（paradoxical brain embolism）という．PFO は正常者でも 26%存在し[4]，通常では右房圧は低いため卵円孔は閉じているが，バルサルバ負荷をすると右房圧が高まり，その後バルサルバ解除をすると卵円孔が開く．若年者の原因不明の脳梗塞症例では卵円孔は約 50%前後認められ[5]，奇異性脳塞栓症が多いと考えられている．右左短絡の診断は，経食道心エコー（transesophageal echocardiography：TEE）で行うのが一般的[3]であるが，侵襲を伴うので高齢者では行いにくいのが現状である．

TCD でマイクロバブル法を用いた右左短絡の診断は，コントラスト TCD といい，撹拌したマイクロバブルを含む生理食塩水を静脈注射して脳

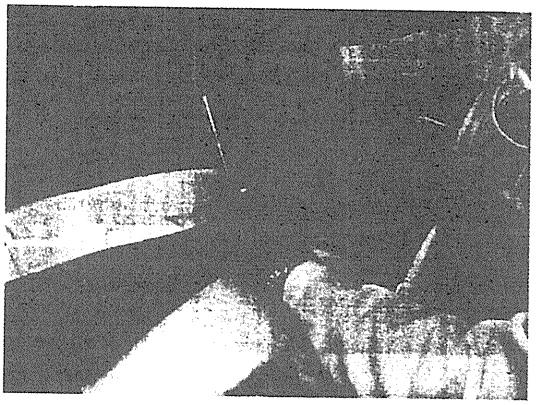

図4　マイクロバブル法
10 cc の注射器2本と三方活栓でつないだトンボ針を静脈に挿入．6 cc の生理食塩水と1 cc の空気を2本の注射器で撹拌する．泡で白く濁った生理食塩水を注射する．

動脈で ES を検出する方法である．**図4**のように，生理食塩水を2本のシリンジで撹拌し（生理食塩水 6〜9 cc，空気 1 cc），泡立てた生理食塩水を右正中静脈に注射する．マイクロバブル静注しはじめて5秒後にバルサルバ負荷を5秒間行い，解除したあとに ES が出現したら右左短絡があると診断できる[6]．簡単な会話でも腹圧がかかりバルサルバ負荷と同様に右左短絡を起こすことがある．しかし会話等において，バルサルバ負荷をせずに右左短絡を認めた場合は，肺動静脈瘻の可能性があり，TEE では短絡がバルサルバ解除3心拍以内なら PFO，4心拍以上なら肺動静脈瘻と診断[2]する．ジアゼパムを1滴加えると，気泡が多くなるため，右左短絡の検出率が高まる[2]．右左短絡の検出率の報告は，TEE より TCD のほうが優れる[7]と報告されていたが，座位での検査ではほぼ同等[8]であり，座位と臥位では右左短絡の検出率は変わらないが ES 量は増える[9]との報告もあり，右左短絡の検索は座位での検査が推奨される．奇異性脳塞栓症は，急性期では肺梗塞も軽度ながら合併しているため右房圧が高く，右左短絡が起こりやすいと考えられている．反対に心房細動を合併していると左房・左室圧が高まり卵円孔による右左短絡が生じにくい[10]．

□ TIA・急性期脳梗塞の TCD の意義

無症候性高度頸動脈狭窄患者に TCD を行い，ES の有無により同側の梗塞または TIA 発症をエンドポイントとした前向き研究では，ES あり群では 60 血管中 6 例（10%），ES なし群では 171 血管中 12 例（7%）に同側に梗塞を認め，有意差はなかった[11]と報告されている．しかし頸動脈狭窄で症候性脳梗塞または TIA をきたした患者の後ろ向き試験では，ES 検出率は脳虚血発作と検査までの時間が短いほど陽性率が高かった[12]と報告されている．

発症 72 時間以内の急性期脳梗塞 100 例の TCD の検討では，病側の中大脳動脈（MCA）で 16 例（16%）の患者に ES を認め，そのうちの半数は頸動脈狭窄例であり，心原性脳塞栓症ではほとんど検出されず 1 例のみであり，ラクナ梗塞では検出されなかった[13]．非弁膜性心房細動患者での ES の検討では，脳梗塞急性期には 37 人中 11 人（29%）に ES がみられ，症状のない患者では 10 人中 1 人（10%）にしか ES は認められなかった[14]．

以上より，ES 検出率は脳虚血発症からの経過時間が短いほど高く，さらに症候性頸動脈狭窄例で高いことが示された．

□ 抗血小板薬と TCD での研究

大規模研究で TCD による ES が検討項目に用いられたものに，CARESS（Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis）試験[15]がある．これは，症候性頸動脈狭窄例（50%以上）でのアスピリンとクロピドグレル併用とアスピリン単独の比較試験である．両群とも初日からアスピリン群は 75 mg 内服し，クロピドグレル併用群は初日に 300 mg 内服，翌日から 75 mg 内服し，TCD は内服前と内服 2 日目，7 日目に行い，TCD で ES を検索した．ES はクロピドグレル併用群で 2 日目から ES はアスピリン群に比較して低下し，7 日目でも低下していた．これは，クロピドグレルの初日の大量投与は 24 時間で ES 減少に結びつくことを表している．

まとめ

急性期脳卒中の対応はtPA投与が注目されがちだが，虚血性脳卒中の的確な診断と治療が予後にも反映するため，日本脳卒中学会認定施設をはじめとする急性期脳卒中対応施設ではTCDの活用が大切である．

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Clinical Features and Functional Outcome of Stroke After Transient Ischemic Attack

Takao Hoshino, MD,* Satoko Mizuno, MD,*
Satoru Shimizu, MD, PhD,† and Shinichiro Uchiyama, MD, PhD*

Background: Transient ischemic attacks (TIAs) greatly increase the risk of stroke, but few reports have examined subsequent stroke in patients with history of TIA. *Methods:* This retrospective, hospital-based study included 506 consecutive patients with acute ischemic stroke who were admitted to our hospital. The clinical features and prognosis were compared between patients with and without TIA. Multiple logistic regression analysis was also performed to identify predictors for poor outcome. *Results:* Of 506 patients, 114 (22.5%) had a history of TIA. Compared to patients without previous TIAs (non-TIA group), patients with previous TIAs (TIA group) were significantly more likely to have hypertension (76.3% vs 64.3%; $P = .016$), dyslipidemia (57.0% vs 41.1%; $P = .003$), chronic kidney disease (28.1% *v* 15.1%; $P = .001$), intracranial major artery stenosis (51.8% vs 36.2%; $P = .018$), and large artery atherothrombosis (43.9% vs 28.3%; $P = .002$). There was no difference in the previous use of antithrombotic medications between the groups (36.0% vs 35.2%; $P = .881$). Although stroke severity on admission was similar, poor functional outcome (modified Rankin Scale score ≥4) was significantly more frequent in the TIA group, and history of TIA was an independent determinant of unfavorable outcome on multiple logistic regression analysis (odds ratio 1.46; 95% confidence interval 1.02–2.10; $P = .041$). *Conclusions:* Atherothrombotic stroke with concomitant vascular risk factors were more frequent in the stroke patients with than without previous TIA. Antithrombotic therapy was conducted only in one-third of the patients even after TIA. The stroke patients with history of TIA were at great risk of disabling stroke. **Key Words:** Acute stroke—clinical features—functional outcome—transient ischemic attack.

Transient ischemic attack (TIA) is a widely recognized warning sign for subsequent stroke. However, because the symptoms of this "warning event" disappear in a short time, even without any treatment, they tend to be disregarded or ignored by both patients and their families. For the same reason, even general physicians sometimes attach low priority to such symptoms. However, many clinical studies have shown that patients are at great risk immediately after TIA, and the short-term risk of stroke has been a focus of attention.[1-9] There has been much research showing the need for urgent assessment and treatment of TIA,[10,11] but detailed reports about the status of acute ischemic stroke in patients with a history of TIA are limited. Clarification of the effect of TIA on the subsequent course of recurrent stroke may be extremely useful information in considering strategies for preventing recurrent stroke after TIA. Therefore, a hospital-based study to investigate clinical features

From the *Department of Neurology; and †Medical Research Institute, Tokyo Women's Medical University, Tokyo, Japan.

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Address correspondence to Takao Hoshino, MD, Department of Neurology, Tokyo Women's Medical University School of Medicine, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. E-mail: thoshino@nij.twmu.ac.jp.

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and functional outcomes of acute ischemic stroke patients with a history of TIA compared to those without a history of TIA was conducted.

Materials and Methods

Subjects

A retrospective, hospital-based study was conducted involving 515 consecutive acute ischemic stroke patients hospitalized in the Department of Neurology at Tokyo Women's Medical University Hospital between April 2005 and March 2010. Eligible patients were those within 1 week of the onset of their first symptomatic ischemic stroke and who were independent in activities of daily living with a modified Rankin Scale (mRS) score ≤2 before the stroke. After excluding 9 patients because they were lost to follow-up or moved out of the region, 506 patients were included in the analysis. These stroke patients were divided into 2 groups: 1 with history of TIA (TIA group) and 1 without such history (non-TIA group), and their respective clinical features and outcomes were compared.

Protocol

The ethics committee of our institution approved the protocol of this study. Data were collected from a computerized observational database, imaging data, and medical records of other hospitals or private practitioners. Our clinic keeps a prospective registry of all consecutive patients. We used a standardized case report form and abstracted a number of demographic and clinical variables including date of the event, medical history, risk factors for stroke, previous medications, previous TIA, physiologic, examination findings and neurologic symptoms. We also documented the results of all diagnostic tests and details of treatment performed during hospitalization. The person imputing data was blinded to the purpose of this study.

At the time of hospitalization, demographic characteristics, medication history, risk factors for stroke, and history of TIA were thoroughly investigated, and a blood sample, chest radiograph, electrocardiogram (ECG), and computed tomographic (CT) scan of the head were obtained. A magnetic resonance imaging (MRI) scan or magnetic resonance angiographic (MRA) scan of the head was performed in 501 patients, after excluding those with cardiac pacemakers or other contraindications. These were all performed within 24 hours of hospital admission. The information was also collected from private practitioners and other hospitals by fax or mail. All strokes were diagnosed by stroke neurologists based on neurologic observations and MRI or CT findings. The vascular territories of ischemia were classified as (1) left anterior circulation, (2) right anterior circulation, (3) posterior circulation, or (4) multiple. Assessments were made for severity of the event according to the National Institute of Health Stroke Scale (NIHSS); NIHSS scores range from 0 to 42, with higher values reflecting more severe neurologic deficits.

Ischemic stroke was defined as an episode of focal neurologic deficits with acute onset lasting >24 hours (or lasting <24 hours with imaging evidence of stroke corresponding with current symptoms). TIA was defined as an acute loss of cerebral or ocular function lasting <24 hours and without corresponding imaging evidence of an ischemic lesion. In accordance with the recommendations of international guidelines,[12] all information obtained from the patients, relatives, caregivers, and medical records of our hospital, other hospitals, or private practitioners were evaluated, and a final diagnosis of TIA was based on the consensus agreement of 2 or more board-certified stroke neurologists. Patients with disagreements of the diagnosis of TIA were excluded from this study. Patients who had not undergone brain imaging during or shortly after TIA were also excluded.

Diagnostic tests during hospitalization included carotid artery ultrasound, transthoracic cardiac ultrasound, and Holter ECG in all patients, plus transcranial Doppler ultrasound, transesophageal echocardiography, 3-dimensional CT angiography (CTA), digital subtraction angiography, and cerebral blood flow single-photon emission computed tomography in some patients when clinically indicated. In patients in whom findings suggesting a right-to-left shunt were confirmed, the presence or absence of venous thrombi was checked with leg vein ultrasound or full body contrast CT or magnetic resonance venography. All cardiac evaluations were conducted by trained cardiologists. The treatment regimen for each patient was determined in accordance with the international consensus by a neurologist with experience treating neurovascular disease.

Stroke-related disability/handicap was assessed by an attending doctor of our hospital with the mRS at the 3-month follow-up. When the patients could not attend the follow-up appointment, we contacted their family members or the staff of rehabilitation center or nursing home by phone. Patients who had died by 3 months were scored as mRS score 6. Poor functional outcome was defined as an mRS score ≥4.

Baseline Risk Factors

Body mass index was measured as kg/m^2. Hypertensive patients were defined as those who were receiving antihypertensive treatment at the time of the event, or those with continuing high values of systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg after >1 week had passed since the event. Patients with diabetes mellitus were defined as those who had previously been diagnosed with type 1 or 2 diabetes, or those with fasting blood glucose ≥126 mg/dL

or blood glucose ≥200 mg/dL on 2 random measurements. Patients with dyslipidemia were defined as those who had been receiving lipid-lowering treatment at the time of the event, or those with serum low-density lipoprotein cholesterol ≥140 mg/dL, high-density lipoprotein cholesterol ≤40 mg/dL, or serum triglycerides ≥150 mg/dL. The estimated glomerular filtration rate (eGFR) was calculated from the modification of diet in renal disease formula by the Japanese coefficient; chronic kidney disease (CKD) was defined as an eGFR <60 mL/min/1.73 m^2. Smoking status was determined based on whether or not the patient was a current smoker. Intracranial arterial stenosis ≥50% on MRA, CTA, or angiograms was considered significant. Carotid artery ultrasounds were read by appropriately trained neurologists, and stenosis ≥50% was defined as significant extracranial arterial stenosis. Patients with either significant intra- or extracranial artery stenosis were considered to have major artery lesions. The history of ischemic heart disease (IHD; myocardial infarction or angina pectoris) and peripheral arterial disease (PAD) was recorded, and any kind of medical condition in the past was taken to be a previous condition. Atrial fibrillation (AF) was judged based on 2 or more ECGs taken before or during hospitalization. All patients were invariably under continuous ECG monitoring during the acute phase.

Stroke Subtypes

Subtypes classified by etiology were large artery atherosclerosis (LAA), cardioembolism (CE), small-vessel occlusion (SV), other cause (OC), or undetermined cause (UND), in conformity with the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[13] Stroke subtype was assigned to each patient by pairs of investigators during hospitalization. In cases of discrepancy, the patient records were reviewed by a few senior investigators, and the final categorization was based on their consensus agreement.

Statistical Analysis

Analyses were performed with SPSS software (v 11.0; SPSS Inc., Chicago, IL). Statistical significance for intergroup differences was assessed by the Chi-square test for categorical variables and the Student *t* or Mann–Whitney *U* tests were used for continuous variables. To identify predictors for poor outcome, we performed multiple logistic regression analysis based on a forward stepwise method including all variables with *P* values <.25 in univariate analysis as follows: history of TIA, SBP ≥140 mm Hg, DBP ≥90 mm Hg, major artery stenosis, history of PAD, AF, and NIHSS score at admission. Because of their clinical relevance and potential importance, age ≥75 years, other vascular risk factors (diabetes mellitus, dyslipidemia, CKD, and smoking), history of IHD, previous antithrombotic therapy, and thrombolytic therapy were retained in the final regression model. Stroke subtypes were excluded from the model because LAA and CE have multicolinearities with major artery stenosis and AF, respectively. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. In all analyses, $P < .05$ was considered significant (2-sided test).

Results

Clinical Features

The subjects in this study were 506 acute stroke patients (mean age 68.5 years; 63.6% males). All patients were of Asian descent. Of 506 patients, 114 (22.5%) had a history of TIA. Table 1 shows a comparison of patient characteristics between patients with history of TIA and those without history of TIA. There were no differences between the groups in age, sex, or length of hospitalization. In a comparison of vascular risk factors, the TIA group had significantly higher percentages for hypertension (76.3% vs 64.3%; $P = .016$), dyslipidemia (57.0% vs 41.1%; $P = .003$), and CKD (28.1% vs 15.1%; $P = .001$). There were no differences with regard to diabetes mellitus or current smoking. Patients in the TIA group had a greater number of vascular risk factors (hypertension, diabetes mellitus, dyslipidemia, CKD, and current smoking) than those in the non-TIA group (mean 2.2 vs 1.7; $P < .001$). The TIA group also had significantly more patients with intracranial major artery stenosis (51.8% vs 36.2%; $P = .003$) and a history of PAD (8.8% vs 3.1%; $P = .009$). The prevalence of AF was nearly equal (30.3% vs 27.3%; $P = .476$).

With regard to stroke subtypes, the percentage of LAA was found to be significantly higher in the TIA group than in the non-TIA group (43.9% vs 28.3%; $P = .002$), while there were no differences in the percentages of CE or SV between the groups. Among patients in whom the subtype was OC, 1 of the patients with antiphospholipid syndrome had a history of TIA.

There were no differences between the 2 groups in the distribution of vascular territories of ischemia, in the percentage of patients who had been receiving antithrombotic therapy before the stroke (36.0% vs 35.2%; $P = .881$), or in the median NIHSS score at the time of hospitalization (8 vs 8; $P = .321$).

Functional Outcome

Figure 1 and Table 2 show the patients' status 3 months after stroke onset. Of 506 patients, 153 (30.2%) had a poor functional outcome and 10 died. In the TIA group, 44 of 114 patients (38.6%) had a poor outcome, significantly higher than the 109 of 392 patients (27.8%) in the non-TIA group ($P = .027$). An analysis by subtype showed that 50 of 161 patients (31.1%) with LAA, 29 of 161 (18.0%) with CE, and 19 of 98 (19.4%) with SV had history of TIA, and with all subtypes, the percentage of patients with a poor prognosis was higher in the TIA group than

Table 1. *Clinical characteristics of patients with and without a history of transient ischemic attack*

	All	TIA group	Non-TIA group	*P* value (TIA *v* non-TIA)
No. of patients	506	114	392	
Age, y, mean (SD)	68.5 (14.3)	69.6 (12.2)	68.2 (14.9)	.368
Male	322 (63.6%)	78 (68.4%)	244 (62.2%)	.228
Length of hospital stay, days, mean (SD)	28.5 (19.2)	29.6 (17.6)	28.2 (19.7)	.485
Body mass index, kg/m^2, mean (SD)	23.3 (3.5)	23.6 (3.6)	23.2 (3.5)	.350
Vascular risk factors				
Hypertension	339 (67.0%)	87 (76.3%)	252 (64.3%)	.016
Diabetes mellitus	193 (38.1%)	52 (45.6%)	141 (36.0%)	.062
Dyslipidemia	226 (44.7%)	65 (57.0%)	161 (41.1%)	.003
Chronic kidney disease	91 (18.0%)	32 (28.1%)	59 (15.1%)	.001
Current smoking	119 (23.5%)	32 (28.1%)	87 (22.2%)	.193
No. of vascular risk factors, mean (SD)	1.8 (1.1)	2.2 (1.1)	1.7 (1.1)	<.001
SBP, mm Hg, mean (SD)	147.3 (26.4)	152.4 (26.5)	145.8 (26.3)	.019
DBP, mm Hg, mean (SD)	82.3 (15.2)	84.5 (15.6)	81.7 (15.1)	.086
Major artery stenosis	201 (39.7%)	59 (51.8%)	142 (36.2%)	.003
Intracranial	134 (26.5%)	40 (35.1%)	94 (24.0%)	.018
Extracranial	82 (16.2%)	23 (20.2%)	59 (15.1%)	.191
History of ischemic heart disease	101 (20.0%)	27 (23.7%)	74 (18.9%)	.258
History of peripheral artery disease	22 (4.3%)	10 (8.8%)	12 (3.1%)	.009
Atrial fibrillation	142 (28.1%)	35 (30.7%)	107 (27.3%)	.476
Stroke subtype				
Large-artery atherosclerosis	161 (31.8%)	50 (43.9%)	111 (28.3%)	.002
Cardioembolism	161 (31.8%)	29 (25.4%)	132 (33.7%)	.097
Small-vessel occlusion	98 (19.4%)	19 (16.7%)	79 (20.2%)	.407
Other	25 (4.9%)	1 (0.9%)	24 (6.1%)	.023
Undetermined	61 (12.1%)	15 (13.2%)	46 (11.7%)	.681
Vascular territory of ischemia				
Left anterior	174 (%)	42 (36.8%)	132 (33.7%)	.531
Right anterior	170 (%)	41 (36.0%)	129 (32.9%)	.543
Posterior	150 (%)	29 (25.4%)	121 (30.9%)	.264
Multiple lesions	12 (%)	2 (1.8%)	10 (2.6%)	.623
Previous antithrombotic therapy	179 (35.4%)	41 (36.0%)	138 (35.2%)	.881
Antiplatelet therapy	144 (28.5%)	37 (32.5%)	107 (27.3%)	.283
Anticoagulant therapy	46 (9.1%)	8 (7.0%)	38 (9.7%)	.382
NIHSS, median (IQR)	8 (5-12)	8 (6-12)	8 (5-12)	.321

Abbreviations: DBP, diastolic blood pressure; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; SBP, systolic blood pressure; SD, standard deviation; TIA, transient ischemic attack.

Unless otherwise indicated, figures expressed as n (%).

in the non-TIA group, although the difference was not significant. The results of multivariate analysis showed that history of TIA was an independent predictor of poor outcome at 3 months (OR 1.46; 95% CI 1.02-2.10; P = .041; Table 3). Other significant factors were major artery stenosis (OR 1.63; 95% CI 1.15-2.33; P = .007), AF (OR 1.52; 95% CI 1.04-2.23; P = 0.03), and NIHSS score on admission (OR 1.72; 95% CI 1.56-1.93; P < .001).

Discussion

In the present study, atherothrombotic stroke with concomitant vascular risk factors was more frequent in stroke patients with a history of TIA than in those without a history of TIA. In addition, although the NIHSS score at the time of hospitalization was nearly equal in the 2 groups, there were significantly more patients with poor outcome in the TIA group. On multivariate analysis, a history of TIA was found to be an independent predictor of poor outcome.

In our hospital-based study, the percentage of stroke patients who had experienced TIA was 22.5% (114/506).

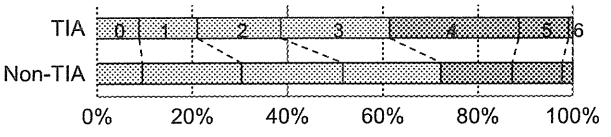

Figure 1. *Distribution of modified Rankin Scale scores 3 months after stroke onset.*

Table 2. *Percentage of poor outcomes at 3 months, overall and by subtype*

	TIA	Non-TIA	*P* value
All (n = 506)			
No. of patients	114	392	
mRS, median (IQR)	3 (2-4)	2 (1-4)	
mRS ≥4	44 (38.6%)	109 (27.8%)	.027
mRS 6	1 (0.9%)	9 (2.3%)	.338
Large artery atherosclerosis (n = 161)			
No. of patients	50	111	
mRS ≥4	24 (48.0%)	39 (35.1%)	.122
Cardioembolism (n = 161)			
No. of patients	29	132	
mRS ≥4	13 (44.8%)	49 (37.1%)	.44
Small-vessel disease (n = 98)			
No. of patients	19	79	
mRS ≥4	2 (10.5%)	3 (3.8%)	.231

Abbreviations: IQR, interquartile range; mRS, modified Rankin Scale.

Unless otherwise indicated, figures expressed as n (%).

Table 3. *Multiple logistic regression analysis for poor outcome*

	OR (95% CI)	*P* value
History of TIA	1.46 (1.02-2.10)	.041
Age ≥75 y	1.26 (0.99-1.77)	.18
SBP ≥140 or DBP ≥90 mm Hg	1.20 (0.86-1.68)	.29
Diabetes mellitus	1.01 (0.79-1.49)	.60
Dyslipidemia	0.98 (0.70-1.37)	.92
Chronic kidney disease	0.94 (0.63-1.39)	.76
Current smoking	1.10 (0.75-1.61)	.61
Major artery stenosis	1.63 (1.15-2.33)	.007
History of ischemic heart disease	0.79 (0.50-1.21)	.28
History of peripheral artery disease	1.49 (0.76-2.91)	.24
Atrial fibrillation	1.52 (1.04-2.23)	.03
Prior antithrombotic therapy	1.08 (0.74-1.58)	.66
NIHSS score on admission	1.72 (1.56-1.93)	<.001
Thrombolytic therapy	0.63 (0.16-2.05)	.50

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; SBP, systolic blood pressure; TIA, transient ischemic attack.

This percentage was particularly high in LAA patients (31.1%). In previous reports, the prevalence of a previous TIA among patients who presented with stroke has been reported to be wide-ranging. The percentage varies, depending on such factors as how TIA is defined, which stroke subtypes are evaluated, and whether the study is population- or hospital-based.[14,15] In the population-based Northern Manhattan Stroke study, the prevalence of TIAs among those who presented with first ischemic stroke was 8.7%.[16] Studies that have included patients with previous stroke, such as the Harvard Stroke Registry and National Institute of Neurological Disorders and Stroke databank, have reported higher rates of TIAs—as high as 50% among those with atherothrombotic stroke.[17,18] However, because TIA was defined without consideration of the presence or absence of imaging findings of stroke, the percentage may be overestimated when a new definition is used.

The percentages of etiologic subtypes among all stroke patients differ greatly by country and race.[19-22] In our study, LAA and CE accounted for about one-third of patients, which is similar to a past report in Japan.[23] Purroy et al[24] investigated the risk of recurrence after TIA with respect to etiologic subtype and reported that the stroke risk was higher in LAA patients than in other subtypes. We also found that there were many LAA stroke patients after TIA, and obtained new findings that their functional outcome was poorer than that of patients who had not experienced TIA. Differences were not significant in an analysis by subtype, but there tended to be more patients with poor outcomes in all subtypes. However, these findings seem to be quite contrary to the conception of "ischemic tolerance." In a number of animal models, reduced impact of ischemia after an initial ischemic insult—ischemic preconditioning—has been shown.[25] The degree of protection from infarction is supposed to be greater with longer duration and greater distribution or severity of the initial ischemia and dependent on the duration between the initial and subsequent injuries. Several clinical studies also have suggested that ischemic strokes are less severe in patients with previous TIA,[26-29] but each has limitations inherent in observational studies. That is, location, duration, and etiology of previous TIA are not always reliable from clinical history and there is no real measure of "dose" or severity of the ischemia. In addition, TIA often precipitates treatment with prophylactic medications, and these medications may impact outcomes. Considering that the condition of artificial ischemia in animal models is different from that of clinical TIA based on multiple vascular risk factors, it may be hard to entirely reconcile with animal studies.

This study had limitations. First, it was a retrospective study. We conducted an analysis based on a computerized database created during the period of patient hospitalization and postdischarge follow-up. Second, because it was a hospital-based study, the characteristics of the cohort may have differed from those of the general community population. These limitations might affect our findings. This study did not investigate the $ABCD^2$ score, length of TIA, territory of TIA, and the time after TIA until stroke recurrence. With regard to multivariate analysis,

prestroke activities of daily living and infectious complications during hospitalization could be confounding factors for poor functional outcome, but the accurate information of these factors was unavailable retrospectively. As to the prestroke activities of daily living, we investigated whether the activity of the patients' daily living had been independent (mRS ≤2) or not. We should have included these factors in the model for precise analysis. It is generally accepted that diabetes[30-32] and CKD[33,34] are associated with poor functional outcome in ischemic stroke, but these factors were not significantly associated with poor functional outcome in our study. The discrepancy might be related to the small sample size and imperfect multivariate model. We included previously diagnosed patients in defining vascular risk factors, and not a few of them had been treated before stroke. We did not take the condition of previous treatment into account, and it potentially affected the results. The subjects of our study seemed to be younger than those of previous reports that revealed a poor outcome in stroke patients with diabetes[30-32] or CKD[33,34]; therefore, the younger age of our subjects might also affect the results. Although additional studies are needed to examine our findings, our study may provide important and useful information in considering stroke prevention strategies in patients with TIA.

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Ulcerated Carotid Plaques with Ultrasonic Echolucency Are Causatively Associated with Thromboembolic Cerebrovascular Events

Tomomi Nakamura, MD,*† Yukiko Tsutsumi, MD,* Yuko Shimizu, MD,* and Shinichiro Uchiyama, MD*

The presence of ulcerated carotid plaques is a risk factor for ischemic stroke, which is associated with thromboembolism. We evaluated the relationship between ulcerated carotid plaques and cerebrovascular events in patients with acute ischemic stroke or transient ischemic attack. We extracted 48 consecutive patients with ulcerated carotid plaques from a cohort of 1111 patients with acute ischemic stroke or transient ischemic attack. All patients were evaluated by carotid ultrasonography and diffusion-weighted magnetic resonance imaging. We defined thromboembolic events by excluding potential cardiac sources of embolism, stroke in posterior circulation, contralateral lesions, and single and small (<1.5 cm) subcortical lesions, and we considered the remaining patients with cortical lesions or multiple or large subcortical lesions as having experienced a thromboembolic cerebrovascular event. We compared ultrasonographic findings in the patients with and those without a thromboembolic cerebrovascular event. A relationship with thromboembolic events was suspected in 10 patients (21%) with ulcerated carotid plaques. The proportion of smokers was significantly higher in the group of patients with a thromboembolic event (90% vs 53%; $P = .03$). Logistic regression demonstrated a significant association between thromboembolic events and the presence of echolucent ulcerated plaques (odds ratio, 9.34, 95% confidence interval, 1.65-53.0), even though maximum intima-media thickness and other variables of ulcerated plaques (eg, depth of ulcers, thickness of the plaque, or the degree of stenosis) did not differ significantly between the 2 groups. Our findings indicate that although cerebrovascular events are closely associated with echolucent ulcerated carotid plaques, the prevalence of thromboembolism was not very high (~20%) in our cohort of Japanese patients with ulcerated carotid plaques. **Key Words:** Ulcerated carotid plaque—ultrasonography—cerebrovascular event—thromboembolism—diffusion-weighted magnetic resonance imaging.

From the *Department of Neurology, Neurological Institute, Tokyo Women's Medical University, Tokyo, Japan; and †Department of Neurology, Itabashi Chuo Medical Center, Tokyo, Japan.

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Address correspondence to Tomomi Nakamura, MD, Department of Neurology, Neurological Institute, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. E-mail: tnakamur@nij.twmu.ac.jp.

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Atherosclerotic carotid artery disease is an established risk factor for ischemic stroke, and the presence of plaques with surface irregularities or ulcerations increases the risk.[1-3] These plaques are more prevalent in patients with a history of stroke or transient ischemic attack (TIA).[4-8] Moreover, the detection of microembolic signals (MES) by transcranial Doppler (TCD) is closely associated with the presence of ulcerated carotid plaques.[9-11] In view of the mechanism of development from ulcerated carotid plaques to cerebrovascular events, ulcerated carotid plaques are considered to be traces of plaque rupture or

fragmentation or sources of emboli generated at the cavity due to stagnated blood flow.[12] The causative relationship between ulcerated carotid plaques and the development of stroke remains controversial, however.[13] Some investigators have reported that ulcerated carotid plaques are not necessarily associated with ipsilateral symptoms, although ulceration is more frequent in symptomatic patients than in asymptomatic patients.[14,15] Another study failed to show correlations between neurologic symptoms and carotid plaque surface irregularities.[16] Yet another study found that the presence of MES is not associated with the characteristics of carotid plaques, even though emboli arose more frequently in symptomatic patients than in asymptomatic patients.[17]

Carotid endarterectomy (CEA) and carotid artery stenting are treatment options for patients with ≥50% stenosis to prevent further cerebrovascular events.[18] But because a causative relationship between cerebrovascular events and ulcerated carotid plaques as a source of thromboembolism (TE) remains obscure, little information regarding treatment for ulcerated carotid plaques is available despite the established risk for ischemic stroke. Diffusion-weighted magnetic resonance imaging (DWI) is the most sensitive tool available for detecting fresh ischemic lesions and identifying the lesions responsible for acute neurologic symptoms. Thus, the use of DWI might help clarify the causative relationship between ulcerated carotid plaques and cerebrovascular events in patients with acute ischemic stroke.

In the present study, we distinguished ulcerated carotid plaques as a source of TE from those without a direct correlation to cerebrovascular events using DWI during the acute phase of ischemic stroke or TIA. We then compared the ultrasonographic findings of ulcerated carotid plaques that were likely to be causatively related to cerebrovascular events with those that were unrelated to these events.

Methods

Patients with ulcerated carotid plaques detected by carotid ultrasonography were enrolled out of a total of 1111 consecutive patients admitted to the Itabashi Chuo Medical Center between January 2005 and December 2008 because of acute ischemic stroke or TIA. All patients were diagnosed with ischemic stroke or TIA by trained neurologists. On admission, each patient underwent a baseline 12-lead electrocardiography, biochemical and hematologic measurements, chest X-ray, magnetic resonance imaging (MRI) including DWI, magnetic resonance angiography (MRA) if without contraindications, and high-resolution duplex carotid ultrasonography. Arrhythmias responsible for cardioembolism, such as paroxysmal atrial fibrillation, were investigated using Holter electrocardiography. The presence of traditional cardiovascular risk factors, including age, sex, hypertension (casual blood pressure ≥160/95 mm Hg or receipt of antihypertensive medication), diabetes mellitus (fasting plasma glucose ≥7.77 mmol/L or receipt of medication), hyperlipidemia (serum total cholesterol ≥5.70 mmol/L or receipt of medication), and cigarette smoking (within the past 5 years or habitually smoking ≥10 cigarettes a day for >1 year, determined from self-report), was recorded. Patients who were diagnosed with TIA without DWI-positive lesions were excluded from the study, because the causative relationship between ischemic brain lesions and ulcerated carotid plaques via TE-related mechanisms could not be clarified.

Carotid Ultrasonography

An experienced examiner who was blinded to patient data performed high-resolution duplex carotid ultrasonography using a 7.5-MHz duplex scanner (Aplio XG; Toshiba, Tokyo, Japan). The common and internal carotid arteries were scanned cross-sectionally and longitudinally, to estimate the presence and distribution of atherosclerotic plaques. The entire common carotid arteries and internal carotid arteries up to approximately 20 mm distal from the tip of carotid bifurcation were scanned bilaterally. Maximum intima-media thickness (IMT) measurements were obtained to identify the thickest region of the arterial wall. Thereafter, the surface appearance of the plaques was scrutinized from several directions. Optimal insonation angles were determined to clearly visualize identified excavations. Ulcers were diagnosed by color-Doppler imaging as the presence of large obvious craters (≥2 mm deep) with a well-defined back wall at the base and reversed or stagnated blood flow in the craters according to an international consensus report.[19]

Carotid plaques with ulcers and the ulcers themselves were analyzed further by ultrasonography. The depth of the ulcers and maximal thickness of the ulcerated plaques were measured (Fig 1). The degree of stenosis at ulcerated plaques was calculated according to the criteria of the North American Symptomatic Carotid Endarterectomy Trial (NASCET).[20] The echogenicity of ulcerated plaques was also evaluated according to previous reports.[19,21] In brief, optimal images of ulcerated plaques were digitized using an Epson ES-8000 scanner (Epson, Tokyo, Japan). Individual ulcerated plaques were then outlined using the computer mouse and analyzed using Adobe Photoshop CS software (Adobe Systems, Mountain View, CA). The gray-scale content (assuming 0-5 for the bloodstream and 185-195 for the intimal lining) was determined and expressed as the mean, median, standard deviation, and total pixel count. The gray-scale median (GSM) was used as a measure of overall plaque echogenicity.[21] Each ulcerated plaque was classified as either echolucent or other based on the GSM value. An echolucent plaque was indicated by a GSM of <50, which was considered equivalent to being uniformly anechoic (class I) or predominantly hypoechoic or anechoic (class II).[19,21]

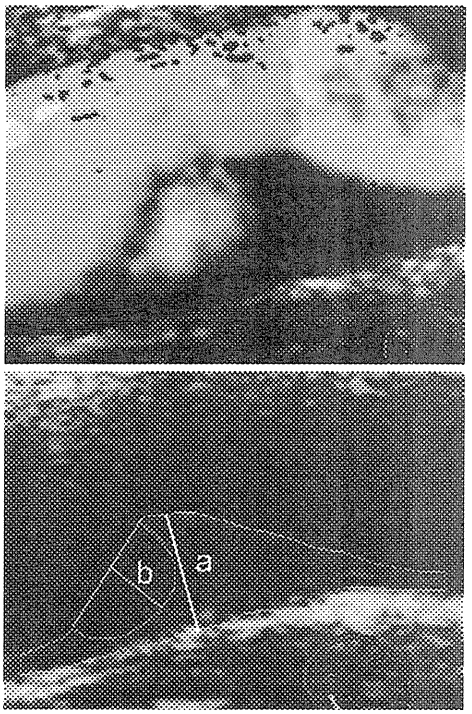

Figure 1. *Example of an ulcerated carotid plaque. Ulcers diagnosed as large obvious craters and reversed or stagnated blood flow within craters on color-Doppler imaging images (upper). The thickness of plaques with ulcers (a) and depth of ulcers (b) were measured at the maximum point (lower). The echogenicity of ulcerated carotid plaques was evaluated by outlining plaques (yellow line) and analyzing gray-scale content.*

Criteria for TE

To identify patients with thromboembolic cerebrovascular events, we excluded patients with ischemic stroke in the posterior circulation confirmed by DWI and those with potential cardiac sources of embolism according to the TOAST (Trial of ORG 10172 in Acute Stroke Treatment) classification from the patients with ulcerated carotid plaques,[22] because a causative relationship between ulcerated carotid plaques and stroke in the posterior circulation or cardioembolic stroke was unlikely. We also excluded patients with DWI-positive lesions contralateral to the ulcerated carotid plaques for the same reason. Finally, we excluded patients with single small (<1.5 cm) DWI-positive subcortical lesions (equivalent to lacunar stroke) because of the low likelihood of an embolus at an ulcerated carotid plaque entering a perforating branch artery from the middle cerebral artery without affecting leptomeningeal arteries.[23,24] We diagnosed a thromboembolic cerebrovascular event in the remaining patients with a cortical lesion or multiple or large (≥1.5 cm) subcortical lesions (Fig 2).

Statistical Methods

Differences in background factors between patients with and without a thromboembolic event were statistically compared using the Student independent *t*-test for age and the χ^2 test for sex and traditional cardiovascular risk factors, including hypertension, diabetes mellitus, hyperlipidemia, and cigarette smoking. Differences in the ultrasonographic characteristics of ulcerated lesions were also compared using the Student independent *t*-test for the maximum IMT, ulcer depth, and ulcerated plaque thickness and the χ^2 test for >50% stenosis of ulcerated plaque and echolucent ulcerated plaque. An association between those plaque features and thromboembolic events was further analyzed using a logistic regression model to determine independent variables as ultrasonographic characteristics of ulcerated lesions. Statistical significance was taken at a level of 5% using SPSS 17.0 (SPSS Japan, Tokyo, Japan).

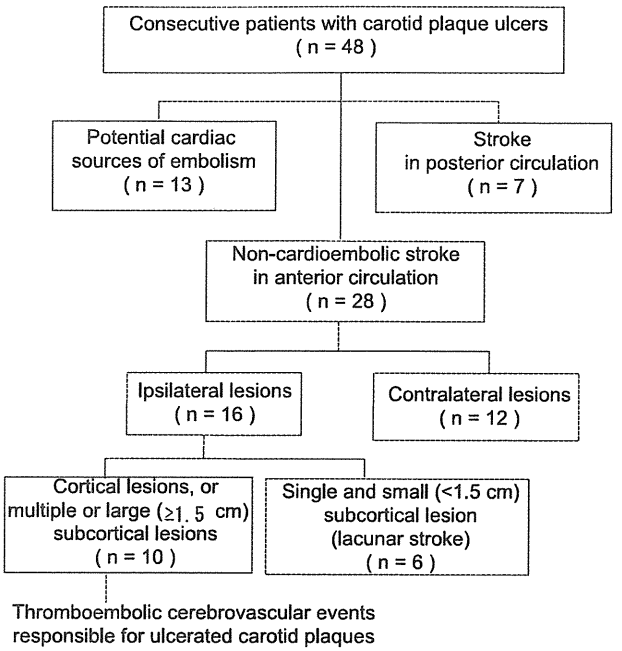

Figure 2. *Criteria for a diagnosis of TE.*

Results

Forty-eight of the 1111 consecutive patients with acute stroke or TIA (4.3%) had ulcerated carotid plaques detected by high-resolution duplex carotid ultrasonography. Among these 48 patients, 13 (27%) had potential cardiac sources of embolism, and 7 (15%) had sustained posterior circulatory stroke. Of the remaining 28 patients with non-cardioembolic stroke in the anterior circulation, 12 (25%) had sustained stroke contralateral to ulcerated carotid plaques and 6 (13%) had small (<1.5 cm) individual subcortical lesions.

Cerebrovascular events were considered causatively related to ulcerated carotid plaques by thromboembolic mechanisms in 10 of the 48 patients (21%) with stroke and ulcerated carotid plaques (Fig 2). Figure 3 shows the DWI images from these 10 patients. Seven of these 10 patients developed symptomatic stroke and 3

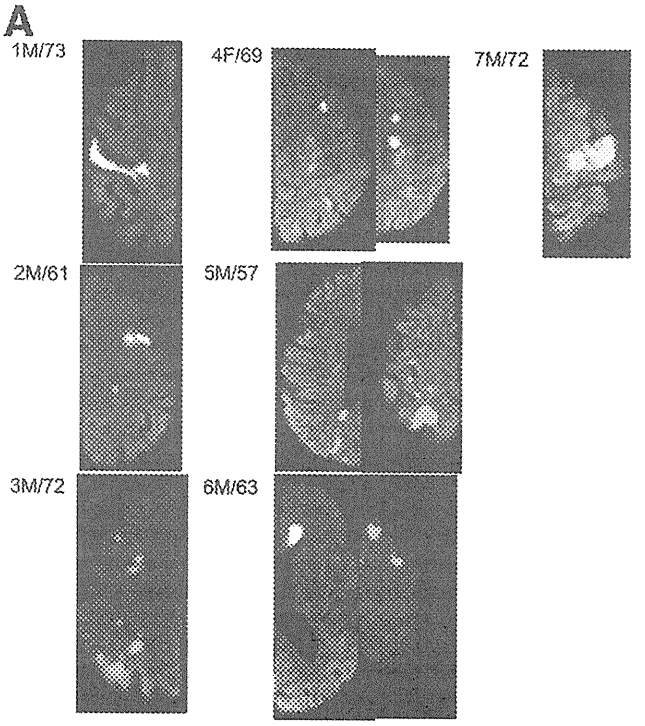

Figure 3. *Diffusion-weighted magnetic resonance imaging in 10 patients with acute ischemic stroke (A) or TIA (B) generated by thromboembolic mechanisms from carotid plaque ulcerations. Numbers indicate patients. Arrows in the TIA images in (B) indicate punctuate high-signal lesions.*

developed TIA, including 1 patient with amaurosis fugax. The patients with DWI-positive lesions were divided into 2 groups based on size and location. All patients in the group with relatively large (≥1.5 cm) single or multiple cortical and/or subcortical lesions (Fig 3A) developed symptomatic stroke, whereas all patients in the other group with punctuated lesions at the cerebral cortex (Fig 3B) developed TIA.

Background characteristics of patients with ulcerated carotid plaques and ultrasonographic ulcer characteristics are presented in Table 1. Univariate analysis found a significantly younger mean age in the patients with a thromboembolic event compared with those without a thromboembolic event (68 ± 8 years vs 77 ± 9 years; $P = .005$). Although all cardiovascular risk factors were more frequent and the proportion of smoking was significantly higher in the patients with a thromboembolic event (90% vs 53%; $P = .03$) events, maximum IMT as an indicator of individual atherosclerotic degree did not differ between the 2 groups. On the other hands, the proportion of echolucent ulcerated carotid plaques was significantly higher among patients with than without thromboembolic events (70% vs. 24%; $P = .006$). Other features of ulcerated carotid plaques did not differ significantly between the 2 groups. We also compared the ultrasonographic features of ulcerated plaques using a logistic regression model and found a significant association between thromboembolic cerebrovascular events and echolucent ulcerated plaques (odds ratio, 9.34; 95% CI, 1.65-53.0), with no significant difference in other variables (Table 2).

Discussion

In the present study, 48 of 1111 patients with stroke or TIA (4.3%) had ulcerated carotid plaques detected by high-resolution duplex carotid ultrasonography. A previous Japanese ultrasonographic study reported the presence of ulcerated carotid plaques in 21 of 214 patients (10%) with at least one risk factor for stroke and atherosclerosis or a history of stroke.[1] Another Japanese study using ultrasonography showed that 52 of 1076 patients (4.8%) had ulcerated carotid plaques at the time of carotid ultrasound assessment of secondary stroke prevention or perioperative risk evaluation.[25] Two major studies outside Japan have described the frequency of ulcerated carotid plaques based on angiographic data. The European Carotid Surgery Trialists (ECST) study identified carotid plaque ulcerations in 14% of 3007 symptomatic carotid arteries in patients with TIA or minor stroke,[26] and the NASCET study found ulceration in 35% of symptomatic carotid arteries with >70% stenosis.[2] Extracranial carotid artery disease is more prevalent in Western populations than in Asian populations,[27] and thus the frequency of thromboembolic cerebrovascular events might be more prevalent in Western populations.

According to our criteria for thromboembolic cerebrovascular events, the proportion of patients with ischemic lesions attributable to carotid ulcers was unexpectedly low (~20%) among patients with ulcers and ischemic stroke or TIA. Although the presence of ulcerated carotid plaques is an established risk factor for ischemic stroke,[1-3] our findings imply that ulcers are not frequently